REMARKS

Applicants have cancelled Claim 32 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 34 to substitute "tag polypeptide" for "epitope tag." Support for this amendment can be found, for example, on page 45, lines 9-15. Applicants have added new Claims 36 and 37. Support for these claims can be found, for example, in the claims as originally filed.

Applicants thank the Examiner for her careful review of the instant application. Claims 27 and 33-37 are presented for examination. Applicants respond below to the rejections set forth in the final Office Action dated March 22, 2005.

Rejection under 35 U.S.C. § 101 – Utility

The PTO rejects Claims 27, and 32-35 under 35 U.S.C. § 101 as lacking patentable utility, for the reasons stated in the Office Action dated February 9, 2004. In that Office Action, the PTO relied on Sen, (Curr. Opin. Oncol. (2000) 12:82-88) and Pennica et al., (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) for the assertions that a slight amplification of a gene does not necessarily result in increased gene expression and increased polypeptide expression, but can merely be an indication of aneuploidy. The PTO concluded that "[t]herefore, data pertaining to PR01800 nucleic acids do not necessarily indicate anything significant regarding the claimed PR01800 polypeptides" and further research is required to determine whether PR01800 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic. Office Action dated February 9, 2004 at 4-5 (emphasis added).

Applicants submit that the evidence in the record, in addition to evidence submitted herewith, illustrate gene amplification correlates with increased levels of the encoded gene product, and confirm that Applicants have established a credible, substantial and specific utility for the claimed polypeptides.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular

practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted

> utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene amplification, gene expression and protein expression (see below). Were there no reasonable correlation between the gene expression and protein expression in particular, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene amplification, gene expression and protein expression. Instead, Applicants' position detailed below is that a gene amplification and increased gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly lung cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that the DNA encoding the PRO1800 polypeptide is amplified in lung tumors, and in a significant number of samples the amplification is greater than four-fold (Ct value greater than 2.0).

2. Applicants assert that there is a sufficient correlation between gene amplification and increased gene expression such that it is more likely than not that the PRO1800 gene is overexpressed in a significant number of lung tumors. This assertion is supported by the declaration and evidence submitted herewith (attached as Exhibit 1) showing overexpression of the PRO1800 mRNA in a significant number of lung tumors and no normal lung tissue samples;

3. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

4. Given Applicants' evidence that the PRO1800 gene is amplified, and the PRO1800 mRNA is increased in a significant number of lung tumors compared to normal lung tissue, it is more likely than not that the PRO1800 polypeptide is increased in a significant number of lung tumors compared to normal lung tissue, making it useful as diagnostic tool for lung cancer, alone or in combination with other diagnostic tools.

The PTO relies on the following arguments set forth in the Office Action dated February 9, 2004, in response to Applicants' asserted utility:

1. Relying on Sen, (Curr. Opin. Oncol. (2000) 12:82-88) the PTO states that "a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action dated February 9, 2004 at 4 (emphasis added);

2. Relying on Pennica et al., (Proc. Natl. Acad. Sci. (1998) 95:14717-14722), the PTO states that "[t]he literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression, such that the

claimed polypeptides would be useful for diagnosis of cancer or as a drug target." Office Action dated February 9, 2004 at 4 (emphasis added).

3. The PTO concludes that "[t]herefore, data pertaining to PR01800 nucleic acids do not necessarily indicate anything significant regarding the claimed PR01800 polypeptides" and further research is required to determine whether PR01800 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic. Office Action dated February 9, 2004 at 5 (emphasis added).

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B.

First, Applicants submit that the two references cited by the PTO are not sufficient to satisfy the PTO's burden of establishing that it is more likely than not that one of skill in the art would doubt Applicants' asserted utility. Second, Applicants submit that contrary to the standard established by the courts and articulated in the M.P.E.P., the PTO is requiring Applicants establish that gene amplification "necessarily" increases gene expression and protein expression. This is not the standard for establishing utility – the standard is a reasonable correlation. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty**.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

In the present Office Action, the PTO states that "the Examiner has made a prima facie case that the mild amount of gene amplification (approximately 2 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of protein." Office Action at 3. (Applicants note that for a significant number of samples, the amplification is greater than four-

fold, not two-fold). The PTO cites only two references made of record to support the "prima facie" finding.

First the PTO states that Sen, (Curr. Opin. Oncol. (2000) 12:82-88), "teaches that a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 3 (emphasis added). Applicants submit that Sen in no way supports this assertion of the PTO. Nowhere in the reference does it discuss the expression, overexpression, or underexpression, of aneuploid genes. What Sen does teach, is that aneuploidy, including amplification, "is the most prevalent genetic change recorded among over 20,000 solid tumors analyzed thus far." Sen at 82, col. 2, ¶1. However, Sen says absolutely nothing about whether amplification leads to overexpression of the amplified gene. Nothing in Sen is contrary to Applicants' assertion that there is a reasonable correlation between gene amplification and gene overexpression. Thus, there is absolutely nothing in Sen to support the PTO's assertion that Sen teaches "a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue."

The second reference relied on by the PTO to support its assertion that it has established a prima facie case is Pennica et al., (Proc. Natl. Acad. Sci. (1998) 95:14717-14722). The PTO cites the following passage from Pennica:

> An analysis of *WISP*-l gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 3.

Applicants first note that overexpression of *WISP*-3 RNA seen in the absence of DNA amplification is not relevant to the Applicants' asserted utility – Applicants' are not asserting that amplification is the only source of gene overexpression. This leaves the results reported for *WISP*-1, where gene amplification is correlated with overexpression, and *WISP*-2, where gene amplification was apparently not correlated with gene overexpression.

The authors of Pennica offer an explanation for what they obviously viewed as an anomalous result: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the *apparent amplification* observed for *WISP-2* may be caused by another gene in this amplicon." (Pennica at 14722, column 1). Thus, the example of a

lack of positive correlation between gene amplification and RNA overexpression relied on by the PTO may be an artifact. The fact that the authors attempt to explain this anomaly only supports Applicants' argument that the accepted understanding in the art is that there is a direct correlation between gene amplification and an increase in gene expression.

As stated above, the standard for utility is not absolute or even statistical certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. One *apparent* contrary example, when combined with the positive example reported, is not sufficient to prove that a person of skill in the art would have a reasonable doubt that gene amplification is not generally correlated with increased gene expression. The PTO has not shown whether the *apparent* lack of correlation observed for one of the two amplified genes studied is typical, or is merely an exception to the rule of correlation. Indeed, the authors' attempt to explain the lack of correlation suggests that this result is the exception, and not the rule. In summary, Pennica provides one example of a positive correlation between gene amplification and increased gene expression, and one *possible* example of a lack of correlation. Applicants submit that this is insufficient to satisfy the PTO's initial burden of establishing that it is more likely than not that one of skill in the art would doubt Applicants' asserted utility.

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal

evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts discussed below.

The PTO has not offered sufficient arguments or references to establish "that one of ordinary skill in the art would reasonably doubt" that claimed polypeptides can be used as a diagnostic tool for cancer. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to overcome the PTO's evidence. When all the evidence of record is considered, Applicants submit that they have establish that one of skill in the art would more likely than not believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly lung cancer.

Applicants have established that the Gene Encoding the PRO1800 Polypeptide is Amplified in Lung and Colon Tumors compared to Normal Tissue and is Useful as a Diagnostic Tool

As an initial matter, Applicants submit that the gene amplification data provided in the present application are sufficient to establish a specific and substantial utility for the gene encoding the PRO1800 polypeptide, as well as the PRO1800 polypeptide.

Applicants previously submitted the declaration of Dr. Audrey Goddard with exhibits A-G. In her declaration, Dr. Goddard states that a 2-fold increase in gene copy number, i.e., a ΔCt value of 1, is "significant and useful" in detecting cancerous tumors or the diagnosis of cancer. Goddard Declaration, paragraph 7. The gene encoding the PRO1800 polypeptide has a value of 1 or greater in several tumor samples tested, with several greater than 2 (more than four-fold

amplification). Thus, the amplification of the nucleic acid encoding PRO1800 can be used to distinguish cancerous tissue from normal tissue.

In the present Office Action, the PTO has not offered *any* reason to reject Dr. Goddard's declaration, particularly the portions relating to the reliability and significance of the evidence. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). Finally, Applicants remind the PTO that they need **not** provide evidence such that it establishes an asserted utility "as a matter of statistical certainty." M.P.E.P. at § 2107.02, part VII (2004).

Applicants have established that the Accepted Understanding in the Art is that there is a Reasonable Correlation between Gene Amplification and Gene Overexpression

Applicants next address the PTO's argument that the claimed invention lacks utility because "a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid" and because "[t]he literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression." Office Action dated February 9, 2004 at 4 (emphasis added).

As discussed above, evidence of utility does not have to be to an absolute certainty, and therefore there does not need to be a *necessary* connection between gene amplification and gene or protein expression. Rather, there need only be a *reasonable* correlation between the evidence offered and the asserted utility such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.

For the record, Applicants state below the evidence provided which supports Applicants' position that there is a reasonable correlation between gene amplification and gene expression.

The teachings in Genes V, a leading textbook in the field, illustrate that at the time the instant application was filed, it was well known by those of skill in the art that gene amplification leads to overexpression of the corresponding gene product. Benjamin Lewin, Genes V, 5th ed. 1994, pages 1196-1201, previously submitted. In a section entitled "Insertion, translocation, or amplification may activate proto-oncogenes", the text describes various molecular events that

lead to overexpression of a gene product, using the *c-myc* gene as an example. The first mechanism taught is insertion of a retrovirus upstream of the gene which causes it to be driven by a more efficient promoter, resulting in increased mRNA and protein levels. Next, Lewin teaches that chromosomal translocations may bring a gene to a new region where it is actively expressed, resulting in increased gene and protein expression. The third mechanism whereby protein levels of oncogenes are overexpressed is gene amplification. The text emphasizes that the common thread among the different means of activation of proto-oncogenes is that the expression of the gene is increased. Thus, as of 1994, it was well-known in the art that gene amplification is correlated with overexpression of the corresponding mRNA and encoded protein.

Additional information regarding the understanding of those of skill in the art regarding the relationship between gene amplification and protein overexpression at the time the instant application was filed is found in Alitalo (Med. Biol., 62:304-317 (1984), a complete copy of which is submitted herewith as Exhibit 2), and Merlino *et al.* (J. Clin. Invest., 75:1077-1079 (1985), previously submitted). Under the heading "Enhanced Expression of Amplified Oncogenes," Alitalo states that "[i]n **all** cases where they have been studied, the amplified oncogenes have been found abundantly expressed at the mRNA level, roughly in proportion to the amount of DNA amplification (see Table 1)." Alitalo at 313 (emphasis added). Table 2 lists eleven examples of amplified oncogenes where expression levels were examined. In all eleven cases, expression of the amplified oncogene was elevated. Thus, Alitalo clearly teaches that amplification leads to overexpression. Merlino *et al.* studied epidermoid carcinoma cells, and teach that amplification of the EGF receptor gene results in increased levels of EGF receptor mRNA and increased levels of EGF receptor protein. Taken together, the excerpt from Genes V, as well as the Alitalo and Merlino references, establish that as of the filing date of the instant application, those of skill in the art appreciated the correlation between gene amplification and overexpression of the encoded gene product.

The teachings of Genes V, Alitalo, and Merlino are confirmed in several more recent reports that also document the correlation between gene amplification and levels of protein. Applicants submit herewith two more recent studies providing evidence that the teachings referred to above are still widely accepted by those of skill in the art. Orntoft *et al.* (*Molecular and Cellular Proteomics*, 1:37-45 (2002); previously submitted) studied transcript levels of 5600

genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts." Orntoft at 37, column 1, abstract. In addition, Hyman *et al.* (*Cancer Research*, 62:6240-6245 (2002); previously submitted) used CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines. They showed that there is "evidence of a prominent global influence of copy number changes on gene expression levels." Hyman at 6244, column 1, last paragraph.

Additional supportive teachings are provided by Pollack *et al.* (*PNAS*, 99:12963-12968 (2002); previously submitted) who studied a series of primary human breast tumors and found that "[b]y analyzing mRNA levels in parallel, we have also discovered that *changes in DNA copy number have a large, pervasive, direct effect on global gene expression patterns* in both breast cancer cell lines and tumors." Pollack at 12967 at column 1, emphasis added. Their study found that "62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack at 12963, column 1, abstract).

Bahnassy *et al.* (BMC Gastroenterology, 4:22-34 (2004), submitted herewith as Exhibit 7) studied the protein expression of *cyclin D1, cyclin A, histone H3* and *Ki-67*, and assessed the amplification of *cyclin D1*. Bahnassy *et al.* found a "significant correlation between *cyclin D1* gene amplification and protein overexpression" (Bahnassy at 27, column 1). Similarly, Blancato *et al.* (British Journal of Cancer, 90(8), 1612-1619 (2004), previously submitted), report that overexpression of *c-myc* mRNA and c-Myc protein is related to the copy number of the *c-myc* amplification (Blancato at 1613, column 2). Bahnassy and Blancato demonstrate continued evidentiary support for the widely-accepted principle that gene amplification correlates with overexpression of the encoded protein.

Together, these references collectively teach that *it is more likely than not* that gene amplification increases mRNA expression. This evidence establishes that there is a reasonable correlation between gene amplification and gene expression, and one of skill in the art would

believe, to a reasonable probability, that gene amplification would lead to increased gene expression.

The PTO has responded to these references by arguing that their applicability to PRO1800 is questionable. In response to Lewin, the PTO argues that the "issue here is *not* that a gene product has been found to be overexpressed, and an explanation of such is being sought, but rather that a *mild, two-fold* amplification of the DNA that would be transcribed to mRNA, that would be translated to protein. There is no evidence of record that the protein is present at elevated level, and the art would not lead to that expectation, as evidenced by Sen and Pennica." Office Action at 3 (emphasis in original).

As an initial matter, Applicants again note that several of the tumor samples tested showed a greater that four-fold amplification, not merely a two-fold amplification. In addition, for the reasons detailed above, Sen and Pennica do not support the PTO's assertion. Thus, contrary to the PTO's position, Lewin (Genes V) does teach that amplification can lead to increased gene expression.

In response to Alitalo, the PTO states that "Alitalo is discussing *known* oncogene, wherein the DNA is amplified *five to many hundredfold.* PR01800 is neither a known oncogene, nor amplified five to many hundred fold. There is nothing in Alitalo's disclosure that would lead the artisan to conclude that a gene that is amplified two-fold in some cancers either would be expected to be an oncogene, nor would be expected to be accompanied by an increase in protein levels." Office Action at 4 (emphasis in original).

While obviously Alitalo does not discuss PRO1800 directly, and instead focuses on known oncogenes, the reference does provide sufficient evidence that in **all** of amplified genes studied there is a reasonable correlation between gene amplification and mRNA expression. Alitalo also states in the abstract that "Amplification of cellular oncogenes can also augment their expression by increasing the amount of DNA template available for the production of mRNA." This statement is repeated in Figure 1, "Increased amounts of oncogene-specific RNA and protein can also result from an excess of DNA template for transcription acquired through oncogene amplification." Both of these statements point to a general correlation between gene amplification and increased gene expression due to increased DNA template for transcription. Combined with the fact that **all** of the oncogenes studied showed a correlation between gene

amplification and gene expression clearly supports Applicants assertion that there is a reasonable correlation between gene amplification and increased gene expression.

In response to the Merlino reference, the PTO argues that unlike EGF, PRO1800 is not known to be associated with cancer, and "[f]urther, Merlino discloses that the EGF receptor gene was amplified 4-5 fold, not the mere two-fold amplification observed for PRO1800. Further still, the EGF receptor was known to be overexpressed in the cell line studied by Merlino. Applicants have provided no evidence of overexpression of the PRO1800 protein in any of the tested cancer cells." Office Action at 4-5.

While PRO1800 (which was amplified at least four-fold in several samples) is not known to be a growth factor, this is not relevant to Merlino's support of Applicants' asserted utility. Merlino states in the abstract, that "SCC-15 cell line was shown to possess an EGF receptor gene copy number amplified four to five times," that "the level of EGF receptor RNA was found to be elevated four-fold in SCC-15" and that SCC-15 "contained high levels of the EGF receptor as determined by immunnprecipitation via an EGF receptor-specific polyclonal antibody." Thus, Merlino clearly supports Applicants' assertion that gene amplification leads to increased gene and protein expression. There is nothing in Merlino that would lead one of skill in the art to think that this finding is limited to EGF, rather than applying to genes generally.

In response to Bahnassy *et al.*, the PTO argues that based on Applicants' characterization of Bahnassy, only one of the four proteins examined showed a correlation between amplification and protein expression. Applicants' previously mischaracterized Bahnassy, implying that the authors looked at both amplification and expression of all four genes. In fact, the authors only examined gene amplification for one gene, *cyclin D1*. (See Methods section, page 3, col. 2). As Applicants' indicated, for the one gene where it was examined, Bahnassy found a "significant correlation between *cyclin D1* gene amplification and protein overexpression." Bahnassy at Abstract.

The PTO also argues that Bahnassy is not applicable to PRO1800 because *cyclin D1* is known to be associated with cell cycle regulation and likely associated with cancer. The PTO also states that amplification was 2-10 fold which the PTO states is "higher than found for PRO1800." Office Action at 5.

As to the first point, as stated above with respect to Merlino, the fact PRO1800 is not known to regulate cell cycle is not relevant to Applicants' asserted utility. There is nothing in

Bahnassy that would lead one of skill in the art to think that this finding is limited to cell cycle proteins, rather than applying to genes generally. As to the argument that Bahnassy reported 2-10 fold amplification, while PRO1800 was only amplified two-fold, Applicants again point out that in several samples, PRO1800 was amplified more than four-fold. Nothing in Bahnassy indicates that the correlation only existed in tumors where the amplification was 5-10 fold.

Finally, the PTO argues that the discussion section of the paper clearly indicates that the art at the time the paper was written had not found either consistency or consensus on the assertion that amplification of cyclin D1 as associated with increased protein levels. For support, the PTO quotes page 20, where Bahnassy states "So far, several studies were done to reveal the prognostic significance of cyclin Dl overexpression in various carcinomas, including CRC 1221. However, these studies yielded conflicting results which could be attributed to organ heterogeneity. In our study, patients with tumors that exhibited cyclin D 1 overexpression tended to have poor prognosis." Office Action at 5 (emphasis added). From this statement, the PTO concludes that Bahnassy shows that far more experimentation is required than is present in this specification as originally filed to establish a correlation between protein expression and cancer in the mind of the skilled artisan. Office Action at 5.

Applicants have asserted that because gene amplification generally leads to increased mRNA and protein levels, the claimed polypeptides are useful to distinguish normal lung tissue from lung tumors. The fact that cyclin D1 may or may not be useful in assessing the prognosis of a cancer patient says nothing about its use as a diagnostic marker. Given the reported correlation between gene amplification and protein overexpression, Applicants submit that Bahnassy supports Applicants' asserted utility.

In conclusion, the PTO states that "the preponderance of the art supports the *prima facie* finding that a minor amplification of DNA would not form the basis for a substantial assertion of an association between PRO1800 protein and cancer." Office Action at 7. As explained above, Applicants' references provide sufficient evidence that in a vast number of amplified genes studied there is a reasonable correlation between gene amplification and increased mRNA expression. In contrast to this evidence, the PTO has submitted a single reference with one *possible* contrary example. When the totality of the evidence is considered, one of skill in the art would believe, to a reasonable probability, that the reported amplification of the PRO1800 gene would lead to an increase in the level of PRO1800 mRNA.

Applicants have established that there is a Reasonable Correlation between Increase in mRNA Levels and an Increase in the Level of the Encoded Protein

Applicants turn next to their assertion that increases in mRNA level, such as those resulting from gene amplification, generally lead to an increase in the level of the encoded protein. The PTO has cited four references which it argues supports the rejection, and indicates that "a two-fold amplification at the DNA level would not be expected to be predictive of protein amplification." Office Action at 6.

First, the PTO cites Hu *et al.* (J. Proteome Res. (2003) 2:405-12). In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu' s findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature"

toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer. And most importantly, Hu says nothing about the relationship between changes in gene expression and changes in the level of the corresponding protein.

The second reference cited by the PTO is Hanna *et al.*, which the PTO assets shows "that gene amplification does not reliably correlate with polypeptide over-expression." Office Action at 6. Hanna describes two methods of testing HER-2/neu in breast cancer: immunohistochemistry (IHC), and fluorescent in situ hybridization (FISH). IHC measures protein levels, while FISH measures amplification levels. Contrary to the PTO's assertions, Hanna actually states that "[i]n general, FISH and IHC results correlate well." Hanna at page 1, col. 2, ¶3. Hanna goes on to describe a subset of tumors where the results do not correlate, but the Hanna clearly supports Applicants' position that, in general, gene amplification leads to overexpression of the encoded protein.

The third reference cited by the PTO is Orntoft *et al.* Applicants understand the PTO to be arguing that because Orntoft only studied well-resolved and focused abundant proteins, and PRO1800 is not known to have these characteristics, this reference offers no support for Applicants. Even if this were true, Orntoft is not contrary to Applicants' position. To the contrary, Orntoft reports that with a few exceptions, "we found a good correlation ($p<0.005$) between transcript alterations and protein levels." Orntoft at Abstract. This clearly supports Applicants' assertion of a general correlation between changes in mRNA level and changes in the corresponding protein level.

Finally, the PTO cites Hyman, which the PTO characterizes as finding that 44% of highly amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed gene being amplified. In addition the PTO states that the article discloses that of 12,000

transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification (2%). Based on these statements, the PTO concludes that gene amplification and gene overexpression do not correlate, and that the "2% does not provide a reasonable expectation that a slight amplification of PRO1800 would be correlated with elevated mRNA, much less protein. Hyman does not examine protein expression." Office Action at 7.

Applicants first note that because Hyman does not examine protein expression, as the PTO acknowledges, it is not contrary to Applicants' assertion that changes in mRNA level are correlated with changes in protein level. Second, Applicants have not asserted that all overexpression, either of the mRNA or a protein, is caused by gene amplification. There are obviously other mechanisms (e.g., translocations) which can lead to overexpression of a mRNA or protein. Therefore, the finding that only 2% of studied genes had overexpression attributable to gene amplification is irrelevant to Applicants' asserted utility since it says nothing about whether gene amplification leads to mRNA or protein overexpression. Likewise, the fact that only 10.5% of overexpressed genes were amplified is irrelevant. What is relevant is that Hyman teaches that there is "evidence of a prominent global influence of copy number changes on gene expression levels." Hyman at 6244, column 1, last paragraph. This supports Applicants' position that gene amplification leads to mRNA and ultimately protein overexpression.

In conclusion, none of the four references cited by the PTO support the PTO's position, and most support Applicants' asserted utility.

In further support of Applicants' assertion that changes in gene expression lead to corresponding changes in protein expression, Applicants have previously submitted a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." Similarly, the previously submitted declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology states that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." Polakis Declaration, paragraph 6. He cites as supporting evidence not only his years of personal experience, but also results from experiments related to the present application. He reports that for the mRNAs overexpressed in cancer that have been examined, 80% had correspondingly higher levels of the encoded protein. Polakis Declaration at paragraphs 4 and 5.

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 3) and (4th ed. 2002) (submitted herewith as Exhibit 4)). Figure 9-2 of Exhibit 3 shows the steps at which eucarotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 3 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 3 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 3 at 453 (emphasis added). Thus, as established in Exhibit 3, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 4, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 4 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 4 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 4 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 4 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 5) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 6. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 6 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 6 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 6 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 7, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Finally, Applicants submit the Declaration of Victoria Smith, Ph.D., an expert in the field of Molecular Biology, (submitted herewith as Exhibit 1). Dr. Smith states that Exhibit B of her Declaration reports the results of the microarray analysis conducted on the gene encoding PRO1800 (DNA35672) as part of the investigation of several newly discovered DNA sequences. The results indicate that the gene encoding PRO1800 is significantly overexpressed in nine of the eighty lung tumor samples tested compared to the normal lung tissue controls. That is the equivalent of one in every nine samples (11%). In contrast, none of the individual normal lung tissue samples show significant overexpression of the PRO1800 gene. In addition, the average ratio of the lung tumor samples shows a statistically significant difference form the average ratio of the individual normal lung tumor samples ($p<0.01$).

Dr. Smith states that "[i]t is well-established in the art that overexpression of the mRNA for a gene is likely to lead to overexpression of the corresponding protein." Smith Declaration at paragraph 6. She explain that:

> While not every lung tumor sample tested shows overexpression of the PRO1800 gene, the data in Exhibit B indicate that a significant portion of lung tumors do (one in every nine), while none of the normal lung tissue samples show overexpression. Given the known correlation between overexpression of a gene and the corresponding overexpression of the encoded protein, it is very likely that a similar number of lung tumors will overexpress the PRO1800 protein, while normal lung tissue samples will not. Together with the data reported in Example 16 that the gene encoding PRO1800 is amplified in some lung tumors, the results reported in Exhibit B indicate that the PRO1800 gene and protein, as well as antibodies to the encoded protein, can be used to differentiate some cancerous lung tissue from normal lung tissue. Smith Declaration at paragraph 7 (emphasis in original).

Because not all lung tumors show overexpression of PRO1800, it cannot be used to exclude a sample being tested as non-cancerous. However, the PRO1800 gene, protein, and corresponding antibodies are useful as a diagnostic tool for lung cancer, alone or in combination with other tools, since a significant number of lung tumors overexpress the gene and most likely the encoded protein, while no normal lung samples do.

Together, the declarations of Grimaldi, Polakis, and Smith, the accompanying references and data, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. Applicants have provided microarray data showing the increased expression of the gene encoding PRO1800 in a significant portion of lung tumors, and have established that there is a reasonable correlation between expression of the gene and the level of PRO1800 protein. Given the evidence provided by the Applicants which establishes that there is a reasonable correlation between gene amplification, and mRNA and protein expression, one of skill in the art would believe, to a reasonable probability, that the reported amplification of the PRO1800 gene would lead to an increase in the level of PRO1800 protein.

The Instant Case is Similar to the Caveat in Example 12 of the Utility Guidelines

In Example 12 of the Utility Guidelines, the specification discloses a protein, receptor A, which is the binding partner for protein X. The specification does not characterize the isolated protein with regard to its biological function or any disease or body condition that is associated with the isolated protein. In addition, the function of protein X has also not been identified. One of the asserted utilities for receptor A is making monoclonal antibodies to receptor A which can be used as a therapeutic drug to effect control over the receptor. In the analysis of this asserted utility for receptor A, the Utility Guidelines state that "since neither the specification nor the art of record disclose *any* diseases or conditions associated with receptor A, the asserted utility in this case essentially is a method of treating an unspecified, undisclosed disease or condition, which does not define a 'real world' context of use." Utility Guidelines at 66, emphasis added.

The situation in Example 12 is not the situation here. Applicants have demonstrated that the nucleic acid encoding PRO1800 is amplified and overexpressed in at least lung cancer. Thus, unlike the protein in Example 12, PRO1800 **is** associated with a known disease or condition – more specifically, lung cancer.

The present situation closely resembles the caveat discussed at the end of Example 12, where receptor A is shown to be present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells. The Utility Guidelines state that in that situation, "making a monoclonal antibody to receptor A for diagnosing melanoma would constitute a well-established utility." Utility Guidelines at 70. Similarly, here Applicants have provided evidence that it is more likely than not that the PRO1800 polypeptide is expressed at higher levels in certain cancer cells than normal tissue, including additional microarray data showing that the PRO1800 gene is overexpressed in certain tumors. Because the PRO1800 polypeptide is overexpressed in certain tumors, it can be used to make diagnostic antibodies.

Conclusion

Applicants have established that it is the general, accepted understanding in the art that gene amplification leads to increased gene and protein expression. The PTO has offered no significant evidence to the contrary, while Applicants have submitted numerous declarations and references to support their position. Applicants respectfully submit that the totality of the above-cited evidence clearly establishes that those of skill in the art would believe that gene

amplification leads to increased gene expression, and that mRNA levels more likely than not correlate with protein levels. In light of the fact that Applicants need not show a *necessary* correlation between gene amplification, mRNA and protein levels, Applicants respectfully submit that they have rebutted any prima facie case of non-utility and non-enablement the Examiner may have established. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112, first paragraph – Enablement

The Examiner maintains the rejection of Claims 27 and 32-35 under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification, due to lack of utility of the claimed polypeptides. Applicants submit that for the reasons set forth above, the claimed polypeptides have credible, substantial, and specific utility. Thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 16, 2005

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